Ivabradine initiation during vulnerable phase in patients hospitalized for decompensated heart failure
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Abstract: Background – The patients hospitalized for heart failure decompensation are exposed to a high risk of events during and early after hospitalization. Elevated heart rate represents an important risk factor in this category of patients. Ivabradine is a heart rate reduction agent with beneficial effects in chronic heart failure. Objectives – The purpose of this study was to assess the tolerability of early ivabradine administration during the vulnerable phase to unselected hospitalized heart failure patients, in conditions similar to those of current medical practice. Material and methods – A prospective observational study that included 50 consecutive patients with hospitalized systolic heart failure, sinus rhythm and heart rate >70 b/min in whom ivabradine was administered during hospitalization or early after discharge. Clinical data, echocardiography, follow-up events were recorded at baseline and after 6 months of follow-up. Results – Mean age was 60 ± 12 years, heart failure etiology was ischemic in 23 patients (46%) and nonischemic in 27 patients (54%). At baseline 26 patients were in NYHA class III and 24 patients in NYHA class IV, left ventricular ejection fraction was 26±7% and mean resting heart rate was 89±9 b/min. Ivabradine was initiated in the hospital in 35 patients (70%) and early after discharge in 15 patients (30%). Concomitant heart failure therapy at baseline consisted of ACE inhibitors/ARBs in 41 patients (82%), betablockers in 46 patients (92%), furosemide in 50 patients (100%), spironolactone in 40 patients (80%), digoxin in 4 patients (8%). After 6 months of follow-up NYHA class improved significantly (no patient in NYHA class IV, 14 patients in NYHA class III and 34 patients in NYHA class II), heart rate decreased significantly (71±11 b/min, \(p<0.0001\)) and LVEF increased by 5% (31±8%, \(p=0.007\)). At 6 months daily ivabradine dose was 5 mg in 5 patients, 7.5 mg in 1 patient, 10 mg in 26 patients and 15 mg in 15 patients. Ivabradine treatment had to be stopped due to intolerance in 3 patients (6%), bradycardia needing dose reduction was noted in 4 patients (8%) and atrial fibrillation during follow-up occurred in 2 patients (4%). There were no significant differences concerning tolerability according to the moment of ivabradine initiation. Admissions due to heart failure aggravation were noted in 10 patients (20%), 4 deaths were recorded (8%). Conclusions – Early initiation of ivabradine therapy in patients hospitalized for decompensated heart failure, before discharge or early after discharge, is well tolerated.

Keywords: heart failure, decompensation, heart rate, drugs

Adding ivabradine to conventional heart failure therapy in hospitalized heart failure patients during hospitalization or early after discharge is well tolerated.

Rezumat: Premize – Pacienții spitalizați pentru decompensația insuficienței cardiace sunt expuși unui risc crescut de evenimente în timpul spitalizării și precoce după externare. Frecvența cardiacă crescută reprezintă un factor de risc important la această categorie de pacienți. Ivabradina este un agent ce scade frecvența cardiacă și are efecte benefice la pacienții cu insuficiență cardiacă cronnică. Obiective – Scopul acestui studiu a fost acela de a analiza tolerabilitatea ivabradinei administrate în perioada vulnerabilă a pacienții cu insuficiență cardiacă spitalizată. Material și metodă – Acest studiu observațional prospectiv a inclus 50 de pacienți consecutivi cu insuficiență cardiacă sistolică spitalizată, ritm sinusal și frecvență cardiacă medie de repaus 70 b/min cărora li s-a administrat ivabradina în timpul spitalizării sau precoce postexternare. Datele clinice, ecocardiografice, evenimentele clinice au fost înregistrate la intrarea în studiu și după 6 luni de urmărire. Rezultate – Vârsta medie a fost 60 ± 12 ani, etiologia insuficienței cardiace a fost ischemică la 23 de pacienți (46%) și nonischemică la 27 de pacienți (54%). La intrarea în studiu 26 de pacienți au fost în clasa NYHA III și 24 de pacienți în clasa NYHA IV, fracția de ejeție a ventriculului stâng a fost de 26±7% iar frecvența cardiacă medie de repaus a fost 89±9 b/min. Ivabradina a fost inițiată în spital.

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BACKGROUND

The patients admitted for heart failure decompensation represent a population which is exposed to a higher risk of events during hospitalization and early after discharge, up to 6 months. This period is considered the vulnerable phase. Data from studies and registries have shown an increased risk of death or heart failure aggravation in these patients, especially in the first month after discharge. In the United States, the rates of readmission at 30 days are between 20-25%, while at 6 months after discharge there was a 10-15% mortality rate and a 30-40% rehospitalization rate.

Optimization of medical therapy during hospitalization in patients with heart failure decompensation is difficult and at discharge the prescription of evidence-based therapy and the doses used are low.

The increase in heart rate is a physiological response to low cardiac output in patients with decompensated heart failure. However, elevated heart rate may become inappropriate because increasing myocardial oxygen demand and decreasing diastolic filling time might lead to hemodynamic deterioration, ventricular dysfunction and clinical decompensation. Increased heart rate is frequently seen in acute decompensated heart failure and may act as a compensatory mechanism or may be a contributing factor for clinical deterioration. Moreover, it is associated with increased myocardial work load and oxygen demand, reduced ventricular efficiency, and impaired ventricular relaxation.

Data from the EVEREST trial have shown that heart rate at discharge and early after discharge is an important prognostic of outcome. A heart rate >75 b/min was associated with increased mortality, while there was no association with the heart rate on admission. Decreasing the heart rate would therefore seem appropriate in order to lower the event rate. Besides betablockers, a standard therapy for heart failure patients, ivabradine, a pure sinus node inhibitor with heart rate reduction effect, has proven beneficial in chronic heart failure patients with systolic dysfunction. Ivabradine, improving ventriculo-arterial interaction caused by heart rate reduction, seems to contribute to the increase in stroke volume and improved cardiac efficiency thereby preserving cardiac output.

OBJECTIVES

Because the period of hospitalization and the first month after hospitalization represent a higher risk vulnerable period, the purpose of our study was to analyze the tolerability of ivabradine initiated early in decompensated heart failure patients with sinus rhythm and increased resting heart rate.

MATERIAL AND METHODS

This was a prospective observational study that included 50 consecutive patients (40 males, 10 females) admitted for decompensated heart failure in our cardiology department. All patients had LV systolic dysfunction (LVEF < 40%) and sinus rhythm with resting heart rate >70 b/min, and were on guideline-recommended background therapy for chronic heart failure. Ivabradine was initiated either in the hospital (during the index hospitalization), either at the first 2 week follow-up visit after discharge.

At baseline (the moment of ivabradine administration) the demographic data (age, sex), clinical characteristics (weight, blood pressure, heart rate), ECG, echocardiographic examination and laboratory data were recorded. Also, concomitant medication (type of drugs and doses) were recorded at baseline and during follow-up.

Blood pressure was measured at the same arm, after 5 minutes of rest, 2 measurements apart (at 2 minutes interval). Heart rate was measured by pulse palpation and confirmed by ECG recording after 5 minutes of rest. Heart rate values were recorded at admission, at
baseline (ivabradine administration), at discharge and at last follow-up visit. Ivabradine dose was reduced in asymptomatic bradycardia <50 b/min or in symptomatic bradycardia <60 b/min. Ivabradine was stopped in symptomatic bradycardia <50 b/min or in the case of atrial fibrillation occurrence.

Echocardiography was performed by the same investigator, at baseline and at the 6 months examination. Left ventricular ejection fraction was calculated after the Simpson’s rule.

Laboratory data were obtained from the hospital laboratory with the patient fasting.

After the first visit (in hospital or as outpatient), control visits were scheduled at 2 weeks, 4 weeks, 3 months and 6 months. At the 6 month visit, clinical examination, ECG, echocardiography and laboratory tests were repeated. Data from this visit were used as follow-up data.

During follow-up readmissions for heart failure aggravation, atrial fibrillation or other cardiovascular events and deaths were recorded. If patients did not come to the follow-up visit a phone call was made to obtain data about the patient status.

Data were expressed as mean ± standard deviation or percentages, comparisons between baseline and follow-up data were done with Student’s paired t test (for continuous values) or Fisher’s exact test (for categorical values). Statistical significance was considered for 2-tailed p value <0.05. Statistical analysis was performed with GraphPad Prism 6 and Excel statistics. All patients gave their informed consent prior to participation into the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

RESULTS

Mean age of our patients was 60 ± 12 years (range 35-88 years). Heart failure etiology was ischemic in 23 patients (46%) and non-ischemic in 27 patients (54%). 17 patients (34%) had diabetes mellitus, 22 patients (44%) had left bundle branch block, 4 patients (8%) had right bundle branch block, 9 patients (19%) had COPD and 3 patients (6%) had previous stroke (Table 1).

At baseline all patients were in NYHA class III (26 patients) or IV (24 patients). At the last follow-up visit 34 patients were in NYHA class II and 16 patients in NYHA class III, none in NYHA class IV (p <0.0001 compared to baseline).

Blood pressure at baseline was 119 ± 20 mmHg systolic and 78 ± 13 mmHg diastolic. At discharge (for patients in whom ivabradine was initiated during hospitalization) systolic blood pressure was 116 ± 13 mmHg and diastolic blood pressure was 77 ± 8 mmHg. At last follow-up visit blood pressure values were significantly higher compared to baseline: 131 ± 20 mmHg systolic and 84 ± 12 mmHg diastolic (p <0.0001). Left ventricular ejection fraction at baseline was 26 ± 7% and after 6 months increased to 31 ± 8% (p = 0.002) (Table 2).
Mean baseline serum creatinine was 1.14 ± 0.3 mg/dl and mean eGFR was 71±21 ml/min/1.73 m².

During hospitalization patient's weight decreased by a mean of 3 ± 2 kg (from 84 ± 18 to 81 ± 18 kg – p=0.4).

Ivabradine was initiated in the hospital in 35 patients (70%) or 2 weeks after discharge in 15 patients (30%). Mean duration of hospitalization was 7.9 ± 4 days (range 3-24 days) and ivabradine was administered at 4 ± 2 days after admission (range 2-8 days). Initial daily ivabradine dose in the hospital was 5 mg in 7 patients (20%) and 10 mg in 28 patients (80%). In patients with postdischarge administration initial ivabradine dose was 5 mg daily in 2 patients (13%) and 10 mg daily in 13 patients (87%). The lower initial dose was given to older or frailer patients. Patients with in-hospital ivabradine initiation had an admission heart rate of 100 ± 13 b/min, 90 ± 9 b/min at baseline (before ivabradine administration) and 74 ± 8 b/min at discharge. For the rest of the patients heart rate at admission was 90 ± 11 b/min, at discharge 81 ± 7 b/min and at baseline (postdischarge ivabradine administration) 88 ± 9 b/min. At last follow-up visit mean heart rate was 72 ± 12 b/min for the first group (in-hospital ivabradine) and 68 ± 8 b/min for the second group of patients (postdischarge ivabradine). Distribution of heart rate changes before and after ivabradine administration is presented in figures 1 and 2. QRS duration was 124 ± 27 ms at baseline and 120 ± 26 ms at follow-up (Table 2).

Concomitant heart failure therapy at baseline consisted of ACE inhibitors/ARBs in 40 patients (80%), betablockers in 46 patients (92%), furosemide in 50 patients (100%), spironolactone in 40 patients (80%), digoxin in 4 patients (8%). The type of betablockers used consisted of carvedilol (34 patients, mean dose 18.2 mg/day), bisoprolol (7 patients, mean dose 3.2 mg/day) and nebivolol (5 patients, mean dose 3.5 mg/day). Digoxin was used in patients not suitable for betablockers (COPD, low blood pressure). The comparative administration of associated drugs in the 2 groups of patients is presented in Table 3, showing a higher percentage of betablockers and spironolactone use in patients with in-hospital ivabradine administration, but without statistical significance.

During follow-up ivabradine dose was increased in 19 patients. 5 patients received 5 mg/day, 1 patient received 7.5 mg/day, 26 patients received 10 mg/day and 1 patient received 15 mg/day.
and 15 patients (30%) were treated with maximal dose (15 mg/day). Doses received according to the moment of ivabradine initiation are presented in Table 4. At 6 months 29 patients (82%) who received ivabradine during hospitalization received 10 or 15 mg daily, as compared to 12 patients (80%) in whom ivabradine was administered after discharge. It was possible to increase the dose of betablocker in 3 patients and in 6 patients ACE inhibitor dose was increased at the follow-up visits.

Ivabradine treatment had to be stopped due to intolerance in 3 patients (6%): 2 patients presented symptomatic bradycardia <50 b/min and 1 patient presented subjective intolerance (fatigue, general discomfort – 2 weeks after discharge). In 4 patients (8%) ivabradine dose reduction during follow-up was necessary due to asymptomatic bradycardia (< 60 b/min), which was transient after dose decrease; in 1 patient the higher dose could be resumed at the next visit (Table 4). All adverse events occurred after discharge, none was present during hospitalization in patients in whom ivabradine was initiated in the hospital. None of our patients presented visual symptoms.

Atrial fibrillation during follow-up occurred in 2 patients (4%), in 1 patient paroxysmal and in 1 patient permanent (Table 5). In these patients ivabradine was stopped and rhythm or rate control drugs (amiodarone, digoxin) were introduced.

Readmissions due to HF aggravation were noted in 10 patients (20%), 1 patient needed 2 hospitalizations during follow-up. 4 deaths were recorded (8%), 2 sudden and 2 due to progressive heart failure (Table 5).

DISCUSSION

Patients hospitalized for heart failure decompensation represent a group with increased risk of subsequent rehospitalizations and death as compared with chronic heart failure outpatients. This risk is highest during hospitalization and in the first month after discharge and remains elevated up to 6 months after discharge. This period was called “vulnerable phase” and has received special attention in the last years. During hospitalization the main therapeutic target is relieving the congestion. The initiation or uptitration of life-prolonging medications (ACE inhibitors, betablockers, mineralocorticoid antagonists) during hospitalization is a difficult task, due to blood pressure decrease, renal function alteration, volemic instability. That is why at discharge many patients do not receive optimal medical therapy. Moreover, there are patients who do not attend the postdischarge visits, so they remain on the therapy prescribed at discharge, the family physician being not familiar with medication uptitration in systolic heart failure.

There are several factors associated with increased risk of adverse events during the vulnerable period, one of them being heart rate (for patients in sinus rhythm). Studies have shown the elevated heart rate to be a predictor of poor prognosis in such patients. A metaanalysis of the large clinical trials using beta blockers has demonstrated that adequate heart rate control correlates with a better outcome, but in patients with stable chronic heart failure. The use of betablockers in patients with HF decompensation is limited due to the negative inotropic and hypotensive effects of these drugs. Ivabradine has shown to increase survival of patients with chronic stable systolic heart failure when added to betablocker therapy. Compared to betablockers, ivabradine has the advantage of “pure” negative chronotropic effect, without any effect on myocardial contractility, blood pressure or peripheral vascular resistance. Data about the use of ivabradine in acute decompensated heart failure are scarce.

Franke et al. reported the cases of 2 patients with acute heart failure due to acute myocarditis in whom ivabradine was administered. In both patients heart rate...
rate was reduced significantly, weaning from inotrope support was possible, and long term evolution was favorable. In another case report of a patient with acute heart failure and dobutamine-induced sinus tachycardia ivabradine reduced heart rate from 114 to 75 b/min, with a subsequent increase in stroke volume. Dobutamine-induced increase in heart rate was blunted by ivabradine administration in another study, at all levels of dobutamine dosage, thereby reducing heart rate related side effects of dobutamine. Post et al presented the use of ivabradine in a patient with acute myocardial infarction and cardiogenic shock, in whom, 48 hours after introduction of ivabradine, heart rate decreased to 80 b/min and the patient could be weaned out of intraaortic balloon pump and inotropes. In a corresponding clinical study, hemodynamic effects of ivabradine were evaluated in ten patients with advanced heart failure (NYHA III). The authors reported an increase of stroke volume of up to 51% after initiation of ivabradine therapy. In another small study of acute heart failure patients in the context of acute myocardial infarction, ivabradine improved short-term outcomes, with good tolerability.

In the present study ivabradine was initiated either in the hospital, either at the first postdischarge visit in patients with high resting heart rate and normal blood pressure. In-hospital initiation in decompensated heart failure has been reported by Sargento et al which have recently published the results of a pilot study about the safety of ivabradine in 10 patients with advanced heart failure (NYHA III). The authors reported an increase of stroke volume of up to 51% after initiation of ivabradine therapy. In another small study of acute heart failure patients in the context of acute myocardial infarction, ivabradine improved short-term outcomes, with good tolerability.

Patients who received ivabradine during hospitalization in our study had a high baseline heart rate (median 90 b/min), higher than in the ivabradine chronic heart failure trials. In 20% of these patients a lower initial dose was used, but subsequently it could be increased during follow-up: however, the last follow-up visit 11% of patients were on 5 mg daily. Heart rate decreased significantly at discharge, without in-hospital side effects, and remained stable thereafter. During follow-up only 1 patient presented symptomatic bradycardia needing drug cessation, while 2 patients presented transient asymptomatic bradycardia.

The patients with ivabradine initiation at 2 weeks after discharge had a lower admission and discharge heart rate than the previous group. However, at the moment of ivabradine initiation, median heart rate was higher than at discharge. This observation reinforces the recommendation of early follow-up visit (2 weeks) because these patients may remain with increased heart rate and may benefit from earlier heart rate reduction. In these patients bradycardia (symptomatic and asymptomatic) was present in a similar number of patients than in the previous group, suggesting that in-hospital ivabradine initiation is not associated with a decreased tolerability compared to initiation after discharge. However, postdischarge follow-up is important since all side effects appeared after discharge, at different intervals. Heart rate decreased significantly, with a mean of 18 b/min in the patients hospitalized, without any significant decrease in blood pressure. On the contrary, blood pressure values increased during follow-up, despite increase in dose of betablockers or ACE inhibitors in some patients, possibly reflecting a favorable hemodynamic effect of ivabradine therapy.

Clinical improvement was noted during follow-up and the rate of rehospitalizations was lower than that reported in acute heart failure registries, but the low number of patients and the lack of a control group do not allow to make categorical assumptions related to outcome. Symptomatic improvement was associated with improvement in left ventricular function. Previous studies have also shown improvement in systolic function under ivabradine therapy. The low mortality rate at 6 months may due to chance, but it should be confirmed by larger studies.

There was an important percentage of patients with left bundle branch block. In the SHIFT trial, the presence of left bundle branch block did not influence ivabradine tolerability or effect on clinical endpoints. These patients have indication for cardiac resynchronization therapy, however, due to the low accessibility for device therapy in our country, ivabradine may be a useful adjuvant therapy for clinical improvement. During follow-up, QRS duration remained stable in all patients.

Patients were well treated, but the betablocker doses used were low. In patients with decompensated heart failure, increase in betablocker dose is difficult due to possible negative inotropic effect and blood pressure decrease. Adding ivabradine allowed a faster decrease in heart rate at discharge (mean 16 b/min), with subsequent increase in blood pressure during follow-up. Also, in patients where the drug was initiated 2 weeks postdischarge, the heart rate decreased and NYHA class improved during follow-up. In a Scottish heart failure service only <15% of “ivabradine suitable” patients received guideline recommended betablocker doses, showing the need for an effective and
well-tolerated therapy to decrease heart rate\textsuperscript{21}. Therefore, addition of ivabradine in suitable patients may be an alternative in order to achieve a better and faster heart rate control in heart failure patients during the vulnerable phase.

Limitations of the study: the main limitation of our study is the lack of a control group and the low number of patients, which would have allowed us to assess better also the patient's outcomes under ivabradine therapy. Also, the betablocker doses used were low, but they represent commonly used doses at discharge in patients hospitalized for heart failure aggravation. In only a few patients natriuretic peptide levels were determined at admission, so we could not use these biomarkers as markers of heart failure severity in all our study patients, but previous data showed that in-hospital ivabradine administration decreases natriuretic peptide levels at discharge.

CONCLUSIONS

Initiation of ivabradine therapy in patients hospitalized for decompensated heart failure with sinus rhythm and heart rate $>70$ beats/min during the vulnerable phase decreases heart rate and is well tolerated. Larger data would be useful to confirm these effects in order to improve these patient's outcomes.

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Authors’ Contributions:

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Analysis and interpretation of data: Darabantiu, Lala.

Drafting of the manuscript: Darabantiu.

Critical revision of the manuscript for important intellectual content: Christodorescu.

Statistical analysis: Darabantiu, Lala.

Study supervision: Puschita

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